Is Consolidation Chemotherapy after Concurrent Chemo-Radiotherapy Beneficial for Patients with Locally Advanced Non–Small-Cell Lung Cancer?

A Pooled Analysis of the Literature

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Introduction: The purpose of this study was to evaluate whether consolidation chemotherapy (CCT) after concurrent chemo-radiotherapy is beneficial for patients with locally advanced non–small-cell lung cancer (LA-NSCLC).

Methods: We systematically searched PubMed for phase II/III trials published before December 31, 2011, examining survival of LA-NSCLC treated with concurrent chemo-radiotherapy. Median overall survival and other study characteristics were collected from each study and pooled. We extracted log-transformed hazards and standard errors under the assumption that survival follows an exponential distribution, and computed a pooled median overall survival and a 95% confidence interval (CI) using random-effects model. Collected trial arms were categorized as having CCT or not having it, CCT+ and CCT−, respectively.

Results: Forty-one studies were identified including seven phase III studies and 34 phase II studies with 45 arms (CCT+: 25; CCT−: 20). Clinical data were comparable for clinical stage, performance status, cancer histology, sex, and median age between the two groups. There was no statistical difference in pooled mOS between CCT+ (19.0 month; 95% CI, 17.3−21.0) and CCT− (17.9 month; 95% CI, 16.1−19.9). Predicted hazard ratio of CCT+ to CCT− was 0.94 (95% CI, 0.81−1.09; $p = 0.40$). There were no differences between the two groups with regard to grade 3−5 toxicities in pneumonitis, esophagitis, and neutropenia. These models estimated that addition of CCT could not lead to significant survival prolongation or risk reduction in death for LA-NSCLC patients.

Conclusion: The pooled analysis based on a publication basis failed to provide evidence that CCT yields significant survival benefit for LA-NSCLC.

Key Words: Non–small-cell lung cancer, Chemo-radiotherapy, Consolidation chemotherapy, Locally advanced.

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Lung cancer continues to be the leading cause of cancer-related deaths worldwide, with approximately 1.4 million deaths per year.[1] Non–small-cell lung cancer (NSCLC) represents more than 80% of all lung tumors, and approximately 35% of patients with NSCLC present with stage III locally advanced non–small cell lung cancer disease (LA-NSCLC). Previous clinical trials of LA-NSCLC demonstrated that concurrent administration of two cycles of chemotherapy with thoracic radiotherapy (TRT) improved overall survival (OS) compared with radiotherapy (RT) alone and/or sequential chemo-RT.[2–4] Thus the standard treatment for patients with LA-NSCLC is recognized as concurrent chemo-RT with curative intent. Despite recent progress, cure rates remain low for those diagnosed with LA-NSCLC, and the prognosis for the vast majority of LA-NSCLC patients still remains poor. Therefore, new strategies such as radiation methods, radiation dose, optimal chemotherapy regimen, prophylactic cranial irradiation, and molecular targeted agents, are needed to improve clinical outcome.[5] The addition of consolidation chemotherapy (CCT) is another attractive approach.

Recently, close attention has been paid to the efficacy of maintenance chemotherapy after platinum combination chemotherapy for metastatic NSCLC patients and postoperative adjuvant chemotherapy for early-stage NSCLC patients. In fact, several randomized studies and their systematic reviews/meta-analyses have already indicated the efficacy of maintenance[6,7] and adjuvant chemotherapy.[8–10] For LA-NSCLC patients, however, little is known about the efficacy of CCT and few randomized studies have been reported. The Hoosier Oncology Group recently performed a randomized phase III study and reported that CCT with docetaxel increased toxicities without significant survival benefit.[11] There is currently insufficient evidence indicating CCT improves OS of patients with LA-NSCLC.

The purpose of this study is to evaluate, through a pooled analysis of publications, whether CCT after concurrent chemo-RT is beneficial for patients with LA-NSCLC in terms of survival prolongation.

MATERIALS AND METHODS

Literature Search and Data Extraction

We performed a systematic search of PubMed for phase II/III trials examining survivals of LA-NSCLC patients treated with concurrent chemo-RT. All trials that had been reported by December 31, 2011, were targeted. Systematic search was performed using the key words, *non-small cell lung cancer*, *radiation or RT*, *concurrent or concomitant*, *phase II or phase III*. All searches were limited to English language and studies with no less than 30 patients per arm. Chemotherapy regimens scheduled in the concurrent phase were limited to platinum combination therapies. When a study had multiple arms and at least one of them fulfilled the requirements, it was included in our analysis. Studies that did not analyze survival data, or that analyzed only patients with poor performance status (PS; Eastern Cooperative Oncology Group score ≥ 2/Karnofsky score ≤ 70) or high-risk complications, or elderly patients (age ≥ 70 years) were excluded. Studies, in which randomization and survival analyses were performed only on patients with no disease progression after induction chemo-RT were excluded because these trials would strongly be biased toward longer OS. We also excluded trial arms in which surgery or induction chemotherapy was offered in addition to the concurrent chemo-RT.

Collected trial arms were categorized as having (CCT+) or not having (CCT−) CCT. We defined CCT as systemic chemotherapy sequentially performed after concurrent chemo-RT. Arms, in which triweekly carboplatin plus paclitaxel were used after low-dose weekly carboplatin plus paclitaxel with concurrent TRT, were included in CCT+ group in this analysis. CCT+ group was further divided into two patterns of CCT: continuous CCT (CCCT), which continues treatment with at least one of the agents given in the initial therapy and switch CCT (SCCT), which switches to a different agent. For each trial, data on sample size, OS, chemotherapy regimens, doses of RT, delivery of treatment, frequency of grade 3−5 toxicities (neutropenia, leukopenia, esophagitis, pneumonitis, and treatment-related death) were collected. Median OS, and 1-, 2-, and 3-year OS rates were determined using reported data or survival curves. We also recorded data of patient characteristics included in studies (age, sex, histology and stage of cancer, and PS) and study characteristics (trial phase, chemotherapy regimen, and period and region in which study was conducted) to assess heterogeneity across studies.

All phase II/III studies were retrieved independently by two investigators (KT and SY) to assess the reliability of data extraction. After selection of potentially appropriate trials, the investigators reviewed each other's selected trials and excluded inappropriate trials with the agreement of both. Disagreements were adjudicated by a third reviewer after referring to the original articles.

Statistical Analysis

To estimate 95% confidence interval (CI) for median (mOS), the observed mOS was considered as an approximate estimate of the median of an exponential distribution. To examine the bias and validity of this estimation, we compared measured and estimated values of 1-, 2-, and 3-year survival rates and calculated the discrepancy among them by mean prediction error and root mean squared error.[12,13]

For each study, hazard was calculated as the natural logarithm of 2 divided by the mOS. We combined log-transformed hazards and standard errors (SEs) from individual studies and computed a pooled mean and SE of the log-transformed hazard using a random-effects model. Comparison of the pooled survival between CCT− and CCT+ was performed by meta-regression analysis. Because two study characteristics, *region* and *period*, were found to be associated with survival, we performed additional meta-regression analysis adjusted for them. Pooled mOS with 95% CI was calculated as the natural logarithm of 2 divided by the pooled hazard, which was converted back from the pooled log-transformed value computed in the random-effects model. Hazard ratio (HR) was obtained by taking the ratio of the pooled hazards estimated in the meta-regression analysis. The I^2 statistics were used to assess heterogeneity across studies, and I^2 less than 25, I^2 of 25 or more, but less than 50, and I^2 of 50 or more were interpreted as signifying low-level, intermediate-level, and high-level heterogeneity, respectively.[14] The survival benefit of CCT was analyzed in all studies, and also in subgroups according to study character using a forest plot of HRs. We used Student's t test, Kruskal–Wallis test, or Pearson's χ^2 test to examine a difference in the distribution of targeted values among trial arms, or in the proportion of targeted trial arms.

A p value less than 0.05 was considered statistically significant, and all reported p values were two-sided. The Eggers' test and Begg's funnel plots were calculated using Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, NJ). All other statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL) or SAS version 9 (SAS Inc., Cary, NC).

RESULTS

Patient Characteristics and Treatment Administrations in Each Study

We identified 41 studies[2,4,15–53] (7 phase III studies and 34 phase II studies) including 45 arms with 3479

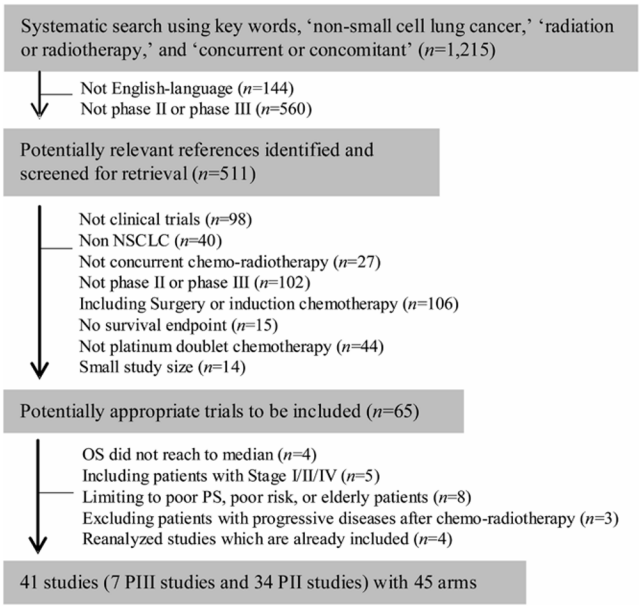

FIGURE 1. Flowchart showing retrieved citations from literature searches and the number of trials analyzed. NSCLC, non–small-lung cancer; PS, performance status.

patients, which examined survivals of LA-NSCLC patients treated with concurrent chemo-RT (Fig. 1; and Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A439). All 41 studies reported mature data on mOS and 1-year OS, whereas 40 studies reported data on 2-year OS, and 32 studies did on 3-year OS.

Among studies analyzed, 25 arms (1707 patients) were designed to perform CCT after concurrent chemo-RT (CCT+ group), whereas 20 arms (1772 patients) were designed for only concurrent chemo-RT (CCT− group). In CCT+ group, four arms (247 patients) were designed for SCCT and other 21 arms (1460 patients) for CCCT. The data on included patients and administered treatments of the two groups are shown in Table 1. There was no statistical difference between the two groups in clinical data of included patients, such as age, sex, histology and clinical stage of cancer, and PS. The planned doses of TRT were comparable between the two groups (62−63 Gy on average in both groups; Table 1). In concurrent phases, approximately 80% to 90% of patients had completed RT/chemotherapy in both groups. Regarding CCT, 1 to 4 (average: 2.3) cycles had been planned in CCT+ arms, and among them, 0.7 to 3.1 (average: 1.5) cycles were actually delivered (Table 1).

TABLE 1. Differences of Patient Characteristics and Treatment Administrations between Study Arms with and without CCT

	Arms without CCT		Arms with CCT		
Patients Characteristics	**Mean**	**SD**	**Mean**	**SD**	***p*[a]**
Age					
Median age	61.71	2.72	60.58	3.24	0.22
Sex					
Female, %	21.96	12.54	23.79	12.92	0.63
Histology					
Squamous cell carcinoma, %	47.56	9.94	43.67	12.20	0.26
Adenocarcinoma, %	35.60	8.85	36.02	12.51	0.90
Stage					
IIIA, %	35.68	19.21	33.19	18.35	0.67
IIIB, %	63.27	19.29	66.31	18.61	0.52
PS, %[b]					
0	46.43	25.72	42.89	19.94	0.65
1	50.38	21.70	52.92	16.01	0.70
2	4.28	6.97	4.36	11.48	0.98
Treatment Administrations					
Concurrent phase					
Planned TRT dose (Gy)	62.85	5.99	62.70	3.50	0.96
Patients who completed TRT (%)	85.65	10.89	89.18	7.66	0.29
Patients who completed chemotherapies (%)	86.15	13.03	79.16	14.47	0.14
Consolidation phase					
No. of planned CCT cycles	—	—	2.32	0.90	—
Median no. of delivered CCT cycles	—	—	1.88	0.90	—
Mean no. of delivered CCT cycles	—	—	1.53	0.64	—

[a]Statistical differences were calculated using Student's *t* test across trial arms.
[b]KPS was converted to Eastern Cooperative Oncology Group PS as follows: KPS 90–100; PS 0, KPS 70–80; PS 1, KPS 60–70; PS 2.
TRT, thoracic radiotherapy; CCT, consolidation chemotherapy; PS, performance status; SD, standard deviation; KPS, Karnofsky performance score.

TABLE 2. Impacts of Study Characteristics on mOS

Study Characteristics	No. of Arms	No. of Patients	mOS		
			Mean	SD	p^a
Trial phase					0.98
II	34	1936	19.36	5.91	—
III	11	1543	19.31	4.27	—
Proportion of stage IIIA patients[b]					0.046
≤33%	22	1674	17.7	3.44	—
>33%	23	1805	20.9	6.64	—
Period					0.022
1995–2000	12	738	16.40	3.80	—
2001–2005	14	978	19.08	4.87	—
2006–2011	19	1763	21.41	6.15	—
Region					0.035
Asian	22	1789	21.12	5.97	—
Non-Asian	23	1690	17.65	4.53	—
Platinum regimens in concurrent phase					0.48
CDDP	29	2524	18.93	5.77	—
CBDCA	16	955	20.11	5.08	—
Employment of third-generation drugs[c]					<0.01
Yes	25	1612	21.12	6.16	
No	20	1867	17.13	3.62	
Use of taxanes[d]					0.33
Yes	18	1122	20.32	5.26	
No	27	2357	18.70	5.67	

[a]Statistical differences were calculated using Student's *t* test or Kruskal–Wallis test across trial arms.
[b]Studies were divided into two groups with the median by proportion of stage IIIA patients.
[c]Third-generation drug was defined as irinotecan, paclitaxel, docetaxel, vinorelbine, gemcitabine, pemetrexed, or S-1.
[d]Taxane was defined as paclitaxel or docetaxel.
CDDP, cisplatin; CBDCA, carboplatin; mOS, median overall survival; SD, standard deviation.

Publication Bias

Potential publication bias was evaluated using the Eggers' test and Begg's funnel plots with log-transformed hazards calculated from mOS (horizontal axis) as the outcome and their SEs (vertical axis) as the index for accuracy (Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JTO/A440). The funnel plots were symmetrical, with *p* values of 0.78, 0.17, and 0.21 in the Egger's test for all study arms, CCT− arms, and CCT+ arms, respectively. These data indicate that there is little evidence of publication bias.

Effects of Study Characteristics on Survival

As our study analyzed potentially heterogeneous study arms with different study characteristics, we next examined the influence of these study characteristics on mOS. We found four characteristics could be implicated in mOS: *proportion of stage IIIA patients*, *region* and *period* in which a study was conducted, and *use of third-generation drugs* (Table 2). As expected, studies which have larger proportion of stage IIIA patients tended to have longer mOS. Studies in Asian countries yielded significantly longer mOS (average: 21.2 month) than those in non-Asian countries (average: 17.7 months), most of which were European countries and the United States. In addition, mOS significantly improved during these 15 years: 16.4 months (1995−2000) versus 19.1 months (2001−2005) versus 21.4 months (2006−2011). Furthermore, studies using third-generation drugs tended to have longer mOS than those using only first- and/or second-generation drugs. Other factors such as *phase II or III* or *platinum regimens (cisplatin or carboplatin) in concurrent phase* did not significantly affect mOS of study arms (Table 2).

The distribution of study characteristics between CCT− and CCT+ is summarized in Supplementary Table 2 (Supplemental Digital Content 3, http://links.lww.com/JTO/A441). Although third-generation drugs were more frequently used in CCT+ than in CCT−, no significant difference was observed in the distribution of other study characteristics (Supplementary Table 2, Supplemental Digital Content 3, http://links.lww.com/JTO/A441).

No Survival Improvement of LA-NSCLC by CCT

mOS and corresponding 95% CI in each study arm are shown in Figure 2. I^2 values for assessing heterogeneity were 15.3, 31.5, and 36.7 in overall, CCT+, and CCT− arms, respectively. No statistical difference was observed in the distribution of mOS between CCT+ and CCT− (p = 0.82). Next, to calculate pooled mOS using random-effects

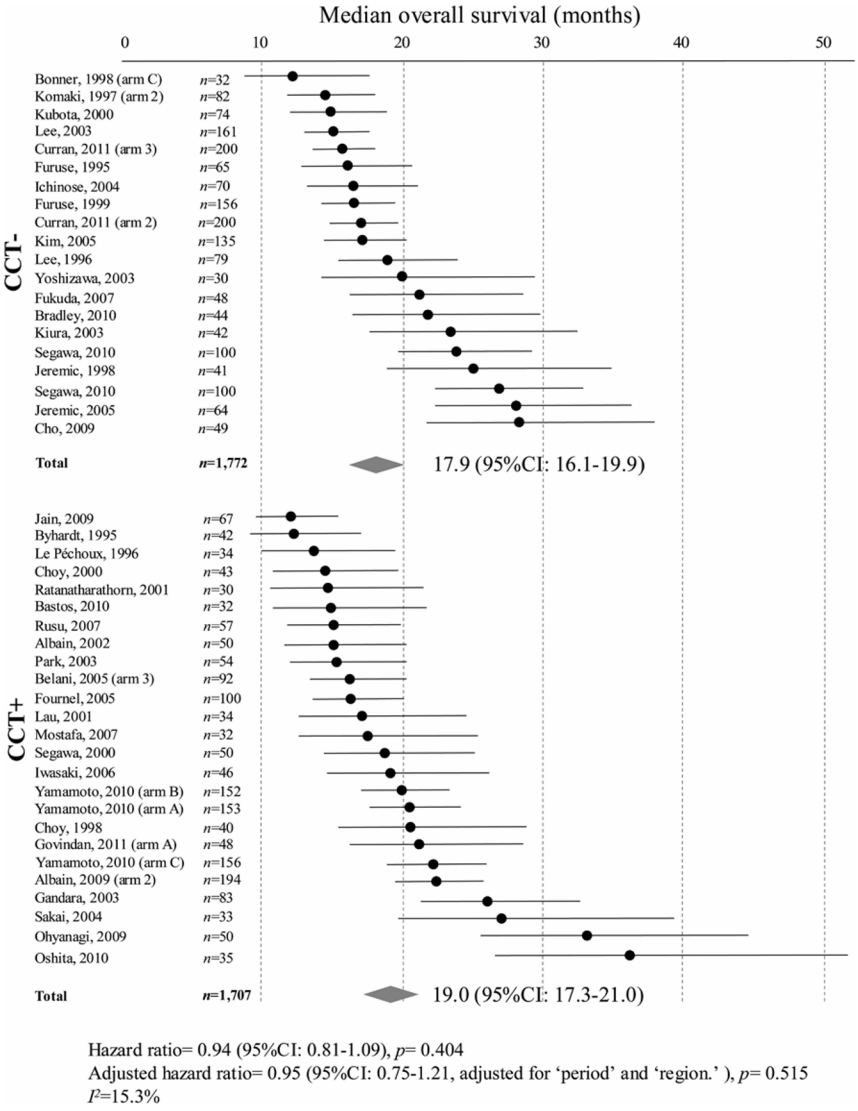

FIGURE 2. Individual and pooled median overall survivals with corresponding 95% CIs in study arms according to the presence of CCT. CCT, consolidated chemotherapy; CI, confidence interval.

models, we estimated that survival follows an exponential distribution. In this assumption, calculated values of 1-, 2-, and 3-year survival rates showed good agreement with actual values of them, with minimal bias and acceptable validity (Supplementary Figure 2, Supplemental Digital Content 4, http://links.lww.com/JTO/A442). In random-effects models, pooled mOS was comparable between CCT+ (19.0 month; 95% CI, 17.3−21.0) and CCT− (17.9 month; 95% CI, 16.1−19.9), and predicted HR of CCT+ to CCT− was 0·94 (95% CI, 0.81−1.09; $p = 0.40$), suggesting that CCT did not significantly improve the mOS of LA-NSCLC patients (Fig. 2). In addition, pooled 1-, 2-, and 3-year survival rates were similar between CCT+ (64.6%, 41.8%, and 27.0%, respectively) and CCT− (62.9%, 39.5%, and 24.8%, respectively), supporting the results of mOS analyses. Similar results were obtained in the additional meta-regression analysis adjusted for four study characteristics that could influence on mOS: proportion of stage IIIA patients, *region* and *period*, and *use of third-generation drugs*, (HR: 0.92; 95% CI, 0.73−1.16; $p = 0.29$). HRs according to study characteristics are shown in Figure 3. CCT did not lead to significant survival benefit in any subgroups analyzed (*period*, *region*, *trial phase*, *proportion of stage IIIA patients*, *use of third-generation drugs*, or *use of taxanes*). Similarly, significant survival advantages were not demonstrated in CCCT or SCCT compared with CCT− (HR: 0.94; 95% CI, 0.81−1.09; $p = 0.424$) and HR: 0.94 (0.71−1.26; $p = 0.694$), respectively, (Supplementary Figure 3, Supplemental Digital Content 5, http://links.lww.com/JTO/A443).

Taken Together, Pooled Analyses on Publication Data Did Not Support Survival Improvement by CCT for Patients with LA-NSCLC

Toxicities

Table 3 summarizes grade 3−5 toxicities reported in the study arms. Toxicities throughout the treatment courses were comparable between CCT− and CCT+ arms. No significant differences were observed in neutropenia, leucopenia, esophagitis, pneumonitis, or treatment-related death.

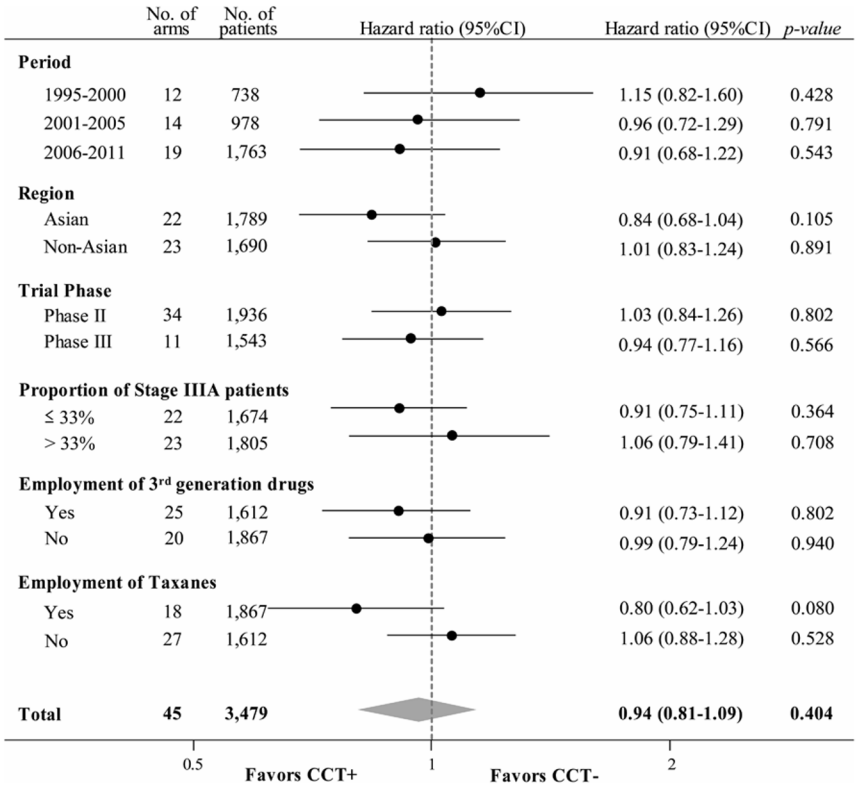

FIGURE 3. Hazard ratios of CCT+ to CCT− in subgroup analysis according to study characteristics. CCT, consolidated chemotherapy; CI, confidence interval.

TABLE 3. Grade 3–5 Toxicities Observed in the Study Arms with and without CCT

	Arms without CCT		Arms with CCT		
Grade 3−5 Toxicities (%)	**Mean**	**SD**	**Mean**	**SD**	***p*[a]**
Neutropenia	50.51	28.42	45.36	24.41	0.63
Leukopenia	58.11	33.11	54.70	22.40	0.74
Esophagitis	14.79	14.68	15.97	12.17	0.78
Pneumonitis	7.97	6.93	7.06	7.30	0.67
Treatment-related death	2.30	2.04	1.96	2.68	0.63

[a]Statistical differences were calculated using Student's *t* test across trial arms.
CCT, consolidation chemotherapy; SD, standard deviation.

DISCUSSION

This pooled analysis on published data did not support the efficacy of CCT in terms of survival prolongation for patients with LA-NSCLC. In this study, the combined mOS of CCT− studies was 17.9 months, which was comparable with that of CCT+ studies, 19.0 months. In addition, the HR of CCT+ to CCT− studies was 0.94. These data suggest that the addition of CCT do not lead to significant survival prolongation or risk reduction in death for LA-NSCLC patients. So far, little is known about the efficacy of CCT after concurrent chemo-RT. Previously, three randomized trials[11,54,55] have been carried out to evaluate the efficacy of CCT for LA-NSCLC (2[54,55] of them have not yet been published as full articles), but all of them failed to show significant survival benefit in CCT arm (Supplementary Table 3, Supplemental Digital Content 6, http://links.lww.com/JTO/A444). Furthermore, we calculated pooled HR using the data of these trials in the same methods described in Materials and Methods, but no significant survival benefit in CCT+ was observed (predicted HR and 95% CI of CCT+ to CCT− were 1.03 and 0.71−1.49, respectively). Combined with these results, our analysis indicates that there is currently no sufficient evidence that supports the benefit of CCT for LA-NSCLC patients. In clinical practice, however, many oncologists still use CCT after concurrent chemo-RT for LA-NSCLC. Moreover, in many ongoing trials, CCT is routinely incorporated, whereas there are few ongoing trials asking the significance of CCT. Further randomized trials will be required to assess the feasibility of using CCT as clinical standard treatment for LA-NSCLC patients. Currently, a phase III study is ongoing in Korea to evaluate the CCT with cisplatin/docetaxel after concurrent chemo-RT with the same agents.[4] The outcome of this study is awaited to assess the significance of CCT for LA-NSCLC patients.

Toxicities induced by CCT are another concern. In previous phase III studies, Hanna and colleagues[11] reported that CCT with docetaxel after concurrent chemo-RT increased toxicities including treatment-related death for LA-NSCLC patients. In this study, however, no difference was observed in toxicities between the two groups. There are several possible explanations regarding this discrepancy. First, our analysis may not able to detect small differences in toxicities because many included studies were not focusing on toxicities in consolidation phase. A second possible explanation is that the number of delivered courses of CCT was lower than planned (Table 1). Third, some chemo-RT regimens used in CCT+ group may have less toxicity. For example, weekly paclitaxel plus carboplatin with TRT followed by two courses of triweekly paclitaxel plus carboplatin has been reported to be less toxic although retaining equivalent efficacy to other full-dose chemo-radiation regimens.[17] Because of less toxic regimens, the toxicities in CCT+ group might have been underestimated. As toxicities mostly depend on the menus and delivered doses/methods of chemotherapy, designs of chemotherapy regimens should be carefully considered for future clinical trials.

This study also highlights two more issues. First, studies conducted in Asian countries, mostly from Japan and Korea, tend to yield longer OS than those in European countries and/or the United States. The finding may be attributable to the ethnic differences between Asian and white patients; an increasing number of publications describe differences in OS and toxicity between Asian and white patients with NSCLC.[56,57] However, why survival of Asian patients is longer than that of white patients has not been clarified, although it may be in part because of the differences among races in tumor behaviors arising from somatic mutations or in sensitivities to drugs/radiation. Of note, the subgroup analyses showed that the HR of Asian studies is 0.84 favoring CCT+, though not statistically significant ($p = 0.105$; Fig. 3). The result may support a possible involvement of ethnicity in the efficacy of CCT. A mechanism underlying these ethnic differences may be a clue to develop a novel treatment strategy for LA-NSCLC. Second, our analyses suggest the improvement in survival outcome of LA-NSCLC patients during the past 15 years. However, this potential survival improvement during this period needs to be assessed with caution, as apparent survival improvement may be influenced by stage migration as a result of advancement in imaging techniques (e.g., positron emission tomography).[58]

This study has several limitations. First, because of the nature of pooled analyses on a publication basis, our analyses included heterogeneous studies with different study designs and various patient populations. Although patient characteristics, trial phase, platinum regimens, study period, and region of the trials did not significantly differ between CCT+ and CCT−, and meta-regression analyses revealed similar results, we cannot exclude the possibility that some other differences might affect our conclusion. In particular, as our analyses were performed on a study basis, they did not cover the heterogeneities in individual patient levels. Second, the impacts of chemotherapy regimens on survival data also remain to be solved. Most studies included in CCT+ were designed for CCCT, and only four studies were designed for SCCT; therefore, the efficacy of SCCT strategy could not be fully evaluated in our analysis, although subset analysis using these four SCCT studies did not show significant survival benefit by CCT. Similarly, we could not clarify the impact of chemotherapy doses on survival, because, in most studies, not full-dose but low-dose/fractionated chemotherapy was offered in the concurrent phase.

Nevertheless, we believe that the findings of this study are relevant because we continue to learn how best to tailor treatment for NSCLC patients. Regarding the treatment of stage IV NSCLC patients, we have experienced a great advance in the last decade; molecular targeted agents and pemetrexed have made a major impact in the selected patients, and molecular profiling has emerged as central to the treatment.[59] In contrast, for LA-NSCLC patients, no significant progress in treatment strategy has been seen during this decade.[60] It seems that we have reached a plateau in survival using current chemotherapy drugs against LA-NSCLC. Therefore, it is urgent to seek new treatment options to improve the prognosis of LA-NSCLC patients. Further clinical studies are vital to establish appropriate CCT regimens, as well as other novel treatment strategies, which lead to survival prolongation and increase in the cure rate of LA-NSCLC patients. Concurrent chemo-RT with no CCT would serve as a reference arm in these trials.

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